CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206494Orig1s000

SUMMARY REVIEW

Division Director Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Memo
NDA #	206494
Applicant Name	Cerexa Inc.
Date of Submission	June 25, 2014
PDUFA Goal Date	February 25, 2015
Established (USAN) Name	Ceftazidime-avibactam
Trade Name	AVYCAZ
Dosage Forms / Strength	Injection/2 grams ceftazidime and 0.5 grams avibactam in single use vials
Indications	1. Complicated urinary tract infections (cUTI), including pyelonephritis for patients who have limited or no alternative treatment options 2. Complicated intra-abdominal infections (cIAI), used in combination with metronidazole for patients who have limited or no alternative treatment options
Recommended Action:	Approval

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Cross-Discipline Team Leader Review	Hala Shamsuddin MD
Pharmacology Toxicology Review	Armand Balboni MD PhD JD Wendelyn Schmidt PhD
Chemistry Manufacturing and Controls Review	Zhengfang Ge PhD
Medical Officer Review	Benjamin Lorenz MD
Statistical Review	Margaret Gamalo PhD
Risk Management	Joyce Weaver Pharm D
Product Quality Review	Robert Mello PhD
Microbiology Review	Avery Goodwin PhD
Clinical Pharmacology Review	Seong Jang PhD
Office of Scientific Investigations	Janice Pohlman MD MPH
Division of Medication Error Prevention and Analysis	Sevan Kolejian Pharm D Justine Harris RPh
Thorough QT Study Review	Interdisciplinary Review Team
Labeling Reviews	Christine Corser Pharm D

1.0 Introduction

NDA 206494, Ceftazidime-avibactam was submitted by Cerexa Inc. on June 25, 2014. The Applicant proposed the following indications:

1. Complicated intra-abdominal infections (cIAI), in combination with metronidazole (MTZ), caused by *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, K. oxytoca, Pseudomonas aeruginosa,* and *P. stutzeri*; and polymicrobial infections caused by aerobic and anaerobic organisms including *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant to ceftazidime-avibactam).

2. Complicated urinary tract infections (cUTI), including acute pyelonephritis, caused by *E. coli* (including cases with concurrent bacteremia), *K. pneumoniae, Citrobacter koseri, Enterobacter aerogenes, E. cloacae, Citrobacter freundii, Proteus spp*. (including *P. mirabilis* and indole-positive Proteus), and *P. aeruginosa*.

3. Aerobic Gram-negative infections with limited treatment options: ceftazidime-avibactam may be used for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP), and bacteremia where limited or no alternative therapies are available and the infection is caused by *E. coli, K. pneumoniae, K. oxytoca, P. aeruginosa, P. stutzeri, P. stuartii, C. freundii, C. koseri, Serratia spp., E. aerogenes, E. cloacae,* and *Proteus spp.,* including *P. mirabilis* and indole-positive *Proteus*. (b) (4)

Since submission of the NDA, the Applicant clarified that they were seeking all the above indications when limited or no alternative treatments are available.

2.0 Background

Ceftazidime-avibactam is a combination of ceftazidime, a third-generation cephalosporin antibacterial drug, and avibactam (formerly NXL104, AVE1330), a non-beta-lactam, beta-lactamase inhibitor (BLI). The avibactam component is a new chemical entity that is not currently marketed in any country, either alone or in combination. Avibactam protects ceftazidime from degradation by beta-lactamase enzymes and maintains the antibacterial activity of ceftazidime against isolates of Enterobacteriaceae and *Pseudomonas aeruginosa* that express

several types of serine beta-lactamases. Avibactam alone has no direct antibacterial activity at concentrations achieved in humans at the proposed dose.

The Investigational New Drug (IND) application was submitted by Novexel in January 2008. Novexel transferred ownership to AstraZeneca Pharmaceuticals LP in April 2010, who then transferred ownership to Cerexa, Inc., a wholly owned subsidiary of Forest Laboratories, Inc. in October 2011. On March 11 2013, ceftazidime-avibactam received qualified infectious disease product (QIDP) and fast track designations for cIAI, cUTI and HABP/VABP. In December 2013, the Applicant and the Agency agreed that a New Drug Application (NDA) covered under Section 505(b)(2) of the Food Drug and Cosmetic Act relying in part on the Agency's previous finding of safety and efficacy of ceftazidime (one of the components of the drug product, ceftazidime-avibactam), could be submitted. Additional data would include nonclinical data, Phase 1 data, data from two Phase 2 trials, and published ceftazidime data. The application also includes safety data on avibactam, including data from patients who received ceftazidime-avibactam. The contribution of the avibactam component is being assessed primarily in in vitro studies and in animal models of infection, where the addition of avibactam restored the activity of ceftazidime against ceftazidime-nonsusceptible bacteria. Ceftazidime-avibactam is a combination product and the contribution of the components was required to be assessed per 21 CFR 300.50. As the components of the combination cannot be studied as monotherapy in the clinical conditions of interest, contribution of the components was assessed in in vitro and in animal models as outlined in the guidance on co-development of two or more investigational drugs for use in combination.[1]

Under the provisions of Generating Antibiotic Incentives Now (GAIN) [Title VIII of FDASIA], NDAs for products with a QIDP designation receive a priority review. As ceftazidime-avibactam has QIDP designation for the submitted indications, it received a priority review. Upon approval, the NDA would be eligible for five additional years of marketing exclusivity under GAIN. The NDA is a PDUFA V 'Program' application as well.

The clinical data in the NDA includes the results of two Phase 2 trials, one each in cUTI (NXL104/2001) and cIAI (NXL104/2002). In both trials, a formal hypothesis for inferential testing was not pre-specified. In addition, the NDA includes interim efficacy results from an ongoing open-label Phase 3 trial in patients with cIAI or cUTI due to ceftazidime-resistant gram negative microorganisms (Resistant Pathogen Study D4280C00006) and a literature review to assess the historical efficacy of ceftazidime in cIAI and cUTI. Also, in October 2014, topline

[1] Codevelopment of Two or More New Investigational Drugs for Use in Combination; http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm236669.pdf; accessed February 04, 2015

results from a recently completed Phase 3 cIAI trial became available and these were submitted to the NDA. Enrollment in a Phase 3 cUTI trial has recently been completed and results are not yet available. Data from the Phase 3 cUTI and cIAI trials will be submitted in the future as supplemental application(s) to support modification of the labeled indications. No clinical data were provided in the NDA to support approval for the "Limited Use" indication of treatment of aerobic gram-negative infections, including HABP/VABP and bacteremia, where limited or no alternative therapies are available. The Applicant proposed this indication based on clinical experience with ceftazidime alone for HABP/VABP, efficacy of ceftazidime-avibactam in (b) (4)

The review team has completed their reviews of this application. For a detailed discussion of NDA 206494, please refer to the discipline specific reviews and the Cross-Discipline Team Leader review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for this NDA is Zhengfang Ge, PhD, and the Product Quality Microbiology reviewer is Robert Mello, PhD.

Avibactam sodium is a new molecular entity and is (b) (4) . The potential genotoxic impurities, (b) (4) are controlled through in-process control and are well below the threshold of toxicology concern. A specified impurity, (b) (4) is qualified at NMT (b) (4)% in the drug substance specification and NMT (b) (4)% in the drug product specification. Dr. Ge found the controls and the qualification of the impurities acceptable. These were also considered acceptable by the pharmacology-toxicology reviewer, Dr. Balboni.

Stability data including 18 months at 25°C/60%RH and 6 months at 40°C/75%RH are provided for three primary avibactam sodium batches. These batches were manufactured at production scale at the proposed commercial manufacturing site ((b) (4)).

Ceftazidime is a semisynthetic cephalosporin antibacterial drug and is manufactured by (b) (4) as a ceftazidime pentahydrate/sodium carbonate blend. The Applicant has cross-referenced Drug Master File (DMF) (b) (4) for CMC information. The DMF was reviewed previously by Dr. Banerjee and found to be adequate on June 28, 2011 for NDA 50578. Amendments received since Dr. Banerjee's review have been reviewed for this NDA and found to be adequate to support this NDA.

The proposed drug product is a sterile, (b) (4) 20 mL, clear, Type I glass vial containing white to yellow powder of 500 mg avibactam ((b) (4) mg avibactam sodium) and 2000 mg ceftazidime (2635 (b) (4) mg ceftazidime pentahydrate/sodium carbonate). No excipients are used in the drug product. (b) (4) Dr. Ge notes that proper in-process controls are proposed to achieve the drug product quality. The identified degradation products include (b) (4) from drug substance avibactam sodium with acceptance criteria at NMT (b) (4) % and (b) (4) from drug substance ceftazidime at NMT (b) (4) %.

The 18-month stability data at 25°C/60% RH and 6 months at 40°C/75% RH provided for three primary drug product batches support a 24-month expiration period. The in-use stability data for reconstituted ceftazidime-avibactam in an infusion bag support a shelf life of 12 hours at room temperature and for up to 24 hours under refrigerated conditions.

Dr. Mello notes that the Applicant has demonstrated adequate controls over the (b) (4) manufacture of the two drug substances and the (b) (4) filling process. The primary container closure integrity study data supporting the sterility maintenance of the final packaged drug substances as well as the drug product was found to be adequate. Post-constitution microbial challenge studies support the preparation and use hold times listed in the product labeling. Dr. Mello recommends approval of the NDA from a product quality microbiology perspective.

The CMC review concluded that the information provided was generally satisfactory to assure the identity, strength, purity, and quality of the drug substances and the drug product. Because of outstanding issues including the pending product quality microbiology review and a final recommendation regarding acceptability of the manufacturing and testing facilities, Dr. Ge did not recommend approval of the NDA when she completed the initial review. On February 23, 2015, the Division of Inspectional Assessment provided an overall recommendation of "Approve" for the facilities.

In an addendum dated February 23, 2015, Dr. Ge recommended approval of the NDA. I concur with Dr. Ge's recommendation.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewers for this NDA are Armand Balboni, MD PhD JD and Wendelyn Schmidt PhD. Most of the nonclinical studies addressed the toxicity of avibactam alone. In rats and dogs, 28-day studies with ceftazidime-avibactam were conducted.

At single intravenous doses of up to 1000 mg/kg, avibactam had minimal effects on behavior, gastrointestinal transit, blood pressure, heart rate, QT interval, or neurologic, renal or respiratory function. A hERG assay was also negative. In toxicokinetic studies, the half-life in rats and dogs ranged from 3-10 hours. Protein binding was less than 25%. Avibactam was distributed primarily into the kidney and bladder in the first few hours following injection, penetration into the brain or across the placenta was minimal. Avibactam was minimally metabolized, was primarily excreted in the urine and did not inhibit or induce cytochrome P450 enzymes.

Single intravenous dose of avibactam up to 2000 mg/kg was identified as the No Observed Adverse Effect Level (NOAEL) in rats and mice. When avibactam was administered to rats or dogs for 4 or 13 weeks, it primarily caused damage to the injection site. The 13-week rat study was difficult to interpret due to presumed *P. aeruginosa* infection from the catheters with observations of multiple organ abscesses and induration. In the 13-week dog study, only injection site damage was seen. Other toxicity studies including local tolerance in the rabbit, human blood hemolysis, immunotoxicology in the rat, and phototoxicity in 3T3 cells were negative.

In the 4-week combination studies of ceftazidime-avibactam (4:1 ratio), injection site damage was seen. There was also some evidence of liver damage in the dog. No new toxicities were seen with the combination product.

Avibactam had no effects on fertility in males or females at the highest dose tested (1000 mg/kg or approximately 20 fold greater than the human dose). However, pre and post implantation loss was increased in females administered avibactam prior to mating at doses greater than or equal to 500 mg/kg (the NOAEL was 250 mg/kg or approximately equivalent to the human dose based on body surface area). Dosing during the period of organogenesis in rats was limited by injection site damage.

In the definitive rabbit fetal development study, the high dose resulted in abortions in a single dam. An increase in late resorptions and decrement in fetal body weights were noted at the high dose of 1000 mg/kg/day. In the rat, the highest dose tested did not show significant maternal toxicity or developmental malformations or variations in the fetuses.

In the rat peri and post-natal toxicity study, there was an increase in the incidence of dilated pelvis and dilatation of the ureter in both individual pups and litter at the high dose of 825 mg/kg/day.

All tests to assess the genotoxic potential of avibactam were negative. Ceftazidime is labeled as being negative in the Ames test and a mouse micronucleus assay. Carcinogenicity testing was not conducted based on the brief duration of use.

Drs. Balboni and Schmidt recommend approval of the NDA from a pharmacology/toxicology perspective. I agree with their assessment.

5.0 Clinical Microbiology

The clinical microbiology reviewer for this NDA is Avery Goodwin, PhD. Ceftazidime binds to penicillin-binding proteins (PBPs) and inhibits cell wall synthesis leading to cell death. Avibactam is a non-beta-lactam beta-lactamase inhibitor that inhibits a broader range of beta-lactamases compared to the currently available beta-lactamase inhibitors such as clavulanic acid, tazobactam, and sulbactam. Avibactam inhibits certain extended spectrum beta-lactamases (ESBLs) of the Ambler class A, C, and D. Avibactam has no activity against the metallo-beta-lactamases. Structurally, avibactam differs from other beta-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam. Avibactam is a [3,2,1]-diazabicyclooctanone derivative that employs a reactive urea rather than a beta-lactam to inhibit serine beta-lactamases.

In in vitro studies, ceftazidime-avibactam demonstrated time-dependent killing, with maximal rates of killing seen at greater than or equal to twice the minimum inhibitory concentration (MIC). The activity of ceftazidime-avibactam was studied in various animal models of infection using ceftazidime nonsusceptible (MIC 8- ≥512 mg/L) isolates of Enterobacteriaceae and *P. aeruginosa*. Activity of ceftazidime-avibactam in relevant animal models of infection is shown in Table 1. In the mouse pneumonia model and the murine thigh infection model, a reduction in bacterial load was demonstrated in animals treated with ceftazidime-avibactam compared to no reduction in bacterial load in animals treated with ceftazidime alone. In a mouse systemic infection model, animals treated with ceftazidime-avibactam had improved survival compared to animals treated with ceftazidime alone. These models demonstrated that the addition of avibactam restored the activity of ceftazidime against ceftazidime-nonsusceptible microorganisms.

Table 1: Activity of Ceftazidime-Avibactam in Animal Models of Infection

Animal Model	Pathogens	Results
Systemic infection Immune-competent mice	Class A and Class C *Enterobacteriaceae*	Survival with ceftazidime: ED_{50} > 50 mg/kg Survival with ceftazidime: ED_{50} 5 to 29 mg/kg
Pyelonephritis Immune-compromised mice	ESBL/AmpC *K. pneumoniae, E. coli*, *E. cloacae*, *M. morganii*, *C. freundii*	Bacterial clearance* in kidney (↓2.6 to 4.5 log_{10})
Murine Thigh infection	*K. pneumoniae* (KPC), *P. aeruginosa*	*K. pneumoniae*:↓bacterial load by >2 log_{10} *P. aeruginosa*: ↓load by ≤1.95 log_{10} (non neutropenic) and ≤ 3.4 log_{10} (neutropenic)

In surveillance studies, the MIC90 values for ceftazidime-avibactam against isolates of Enterobacteriaceae from cUTI in the US in 2012, ranged from 0.12 to 1 mg/L and for *P. aeruginosa* was 4 mg/L and for ceftazidime were 0.5 to >32 mg/L and 16 mg/L for Enterobacteriaceae and *P. aeruginosa*, respectively. The MIC90 values for ceftazidime-avibactam against isolates of Enterobacteriaceae from cIAI in the US in 2012, ranged from 0.06 to 2 mg/L and for *P. aeruginosa* was 32 mg/L and for ceftazidime were 0.5 to >32 mg/L and 16 mg/L for Enterobacteriaceae and *P. aeruginosa* respectively.

In surveillance studies, the MIC90 values for *P. aeruginosa* ranged from 4 to 8 mg/L, with the exception of one surveillance study from Latin America where the reported MIC90 value was 16 mg/L. The MIC90 values for Acinetobacter species ranged from 8 to > 128 mg/L. For gram-positive bacteria including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Streptococcus agalactiae*, the MIC values were similar to that of ceftazidime suggesting that the addition of avibactam did not affect the activity of ceftazidime. Ceftazidime-avibactam is not active against most clinically relevant gram-negative and -positive anaerobic bacteria.

Among the ceftazidime-nonsusceptible isolates from the US, the MIC90 for ceftazidime-avibactam was 16 mg/L in one study and 8 mg/L in a second study compared with > 8 and > 128 mg/L for meropenem and piperacillin-tazobactam, respectively and for non-US isolates, ranged from 8 mg/L in the Middle East and Africa to 64 mg/L in the Asia/Pacific region.

The activity of ceftazidime-avibactam was assessed against 701 ESBL producing organisms out of ~ 6000 isolates of Enterobacteriaceae collected in the US in 2012. CTX-M-15-like enzymes

(43.2%) were the most commonly identified class A beta-lactamase in this study, followed by SHV enzymes (25.1%) and *Klebsiella pneumoniae* carbapenemase (KPC) enzymes (16.8%). The MIC90 values for ceftazidime-avibactam ranged from 0.25-2 mg/L against the confirmed beta-lactamase producers. All isolates were inhibited by ≤ 4 mg/L avibactam including KPC-producing isolates and isolates producing multiple beta-lactamases. The addition of avibactam to ceftazidime appears to have extended the activity of ceftazidime since the ceftazidime MIC90 values ranged from 16 to > 32 mg/L for these isolates.

In avibactam mutant selection studies, frequencies for stable mutants for *P. aeruginosa* and Enterobacteriaceae with ESBL, AmpC or KPC beta-lactamases were assessed and ranged from 2.04×10^{-9} to 1.8×10^{-6}.

Dr. Goodwin agreed with the Applicant's assessment that the combination of ceftazidime-avibactam is capable of overcoming most AmpC-mediated resistance in *P. aeruginosa*, reducing the MIC to levels ≤ 8 mcg/mL and against the Enterobacteriaceae, ceftazidime-avibactam demonstrated activity against Class A, C and some Class D ESBL producing isolates. All Enterobacteriaceae demonstrated ceftazidime-avibactam MIC ≤ 4 mcg/mL.

I agree with Dr. Goodwin's assessment that the data submitted by the Applicant support the findings that ceftazidime-avibactam is efficacious against indicated, susceptible bacterial isolates associated with cIAI and cUTI.

6.0 Clinical Pharmacology

The clinical pharmacology reviewer for this NDA is Seong Jang, PhD. The pharmacokinetics (PK) of ceftazidime and avibactam are linear. Both avibactam and ceftazidime undergo limited metabolism and there is no evidence of a drug-drug interaction between ceftazidime and avibactam. The protein binding of ceftazidime and avibactam is less than 10%. Both ceftazidime and avibactam are primarily eliminated by the kidneys; 80-90% of ceftazidime and 85% of avibactam are recovered as unchanged drug in urine. The terminal elimination half-life (t½) of ceftazidime and avibactam are prolonged in patients with renal impairment. Dose adjustment is needed in patients with creatinine clearance (CrCL) ≤ 50 mL/min. Avibactam is a substrate of human organic anion transporter (OAT) 1 and OAT3 in vitro. The in vitro uptake of avibactam by OAT1 and OAT3 was not inhibited by ceftazidime but was inhibited by probenecid, a potent OAT inhibitor. The clinical impact of potent OAT inhibitors on the PK of avibactam is not known. There is no drug-drug interaction between ceftazidime-avibactam and metronidazole.

Population PK analyses based on data from the Phase 2 cIAI trial, five Phase 1 studies in healthy volunteers, and subjects with impaired renal function showed that the main predictors of clearance (CL) for avibactam and ceftazidime were body surface-normalized creatinine clearance (nCrCl) and CrCL, respectively. For both avibactam and ceftazidime, cIAI was identified as a

significant covariate impacting CL and central volume of distribution. In the cIAI population, the CL and central volume of distribution for both ceftazidime and avibactam were higher compared to healthy volunteers. The population PK model estimated a 34% and 59% decrease in the mean steady state AUC and Cmax for avibactam, respectively, for cIAI patients in the Phase 2 trial with normal renal function compared to Phase 1 subjects with normal renal function. Similarly, the population PK model estimated a 20% and 38% decrease in the mean steady state AUC and Cmax for ceftazidime, respectively, for cIAI patients in the Phase 2 trial with normal renal function compared to Phase 1 subjects with normal renal function.

Patients with CrCL of less than 50 mL/min were excluded from the Phase 2 cIAI trial and those with CrCL less than 70 mL/min were excluded from the Phase 2 cUTI trial. The dosing regimen originally proposed by the Applicant and that used in the recently completed Phase 3 cIAI trial was as follows:

Table 2: Initially Proposed Dosing Regimens

Estimated Creatinine Clearance (mL/min)	Recommended Dosage Regimen
> 50	No dosage adjustment necessary
≥ 31 to ≤ 50	1.25 g IV (over 2 hours) every 12 hours*
≥ 16 to ≤ 30	1.25 g IV (over 2 hours) every 24 hours*
≥ 6 to ≤ 15	0.625 g IV (over 2 hours) every 24 hours§
≤ 5	0.625 IV (over 2 hours) every 48 hours§

*1 gram of ceftazidime and 0.25 grams of avibactam; § 500 mg ceftazidime and 0.125 grams of avibactam

The originally proposed dosing regimen was selected based on probability of target attainment analysis that suggested ~100% probability of achieving the joint PK/PD target (i.e., 50%fT> MIC for ceftazidime and 50%fT > 1.0 mg/L for avibactam) for MICs up to 8 mcg/mL.

In October 2014, the Applicant informed the Agency that ongoing analysis of the Phase 3 cIAI trial showed that in the subgroup of patients with CrCL ≤ 50 mL/min, clinical outcomes in the ceftazidime-avibactam treatment group were much lower than that seen in the meropenem-treatment group. The number of deaths was also higher in the ceftazidime-avibactam treatment group compared to the meropenem treatment group. One possible reason for this difference was thought to be inadequate dosing in patients with rapidly changing renal function.

Additional analyses were performed to assess if the original proposed dosing regimen in patients with renal impairment needed to be modified. PK parameter values using the original proposed dosing regimen were assessed based on simulated cIAI patients. As shown in Table 3, the largest increase in predicted exposure (i.e., C_{max} and AUC) of ceftazidime and avibactam was in the category of mild renal impairment compared to normal renal function. The mean $AUC_{0\text{-}24,ss}$ was 39% higher for avibactam and 52% higher for ceftazidime. However, the predicted $AUC_{0\text{-}24,ss}$ for ceftazidime and avibactam in patients with mild renal impairment (828 mcg·h/mL and 131 mcg·h/mL, respectively) are similar to the values observed following 11 days of dosing with 2.5 grams ceftazidime-avibactam in healthy subjects with normal renal function in Study D4280C00011 (873 mcg·h/mL and 114.6 mcg·h/mL for ceftazidime and avibactam, respectively). The predicted exposures of ceftazidime and avibactam in simulated patients with moderate (CrCL 31 mL/min to ≤ 50 mL/min) and severe (CrCL 6 mL/min to ≤ 30 mL/min) renal impairment receiving the originally proposed dosing regimens were substantially lower than those seen in simulated patients with normal renal function.

Table 3: PK Parameters in cIAI Patients (Using the original proposed dosing regimen)

Renal Function	Proposed Dose Regimen	Ceftazidime		Avibactam	
		$C_{max,ss}$ (µg/mL)	$AUC_{0\text{-}24,ss}$ (µg·h/mL)	$C_{max,ss}$ (µg/mL)	$AUC_{0\text{-}24,ss}$ (µg·h/mL)
NORM	2000 mg CAZ + 500 mg AVI, q8h	47.2±13.4	542±161	9.31±1.87	93.5±21.3
MILD	2000 mg CAZ + 500 mg AVI, q8h	59.9±17.1	828±260	11.2±2.37	131±36.4
MODE	1000 mg CAZ + 250 mg AVI, q12h	33.5±9.6	448±142	6.84±1.48	80.3±22.8
SEV1	1000 mg CAZ + 250 mg AVI, q24h	33.9±10.2	400±136	7.61±1.85	82.8±26.7
SEV2	500 mg CAZ + 125 mg AVI, q24h	27.0±9.03	455±180	6.79±2.07	116±47.6
ESRD	500 mg CAZ + 125 mg AVI, q48h	45.7±22.9	898±527	5.26±1.04	75.6±16.8

NORM (CrCL > 80 mL/min); MILD (CrCL 51 mL/min to ≤ 80 mL/min); MODE (CrCL 31 mL/min to ≤ 50 mL/min); SEV1 (CrCL 16 mL/min to ≤ 30mL/min); SEV2 (CrCL 6 mL/min to ≤ 15 mL/min); ESRD End-stage renal disease (CrCL 0 mL/min to ≤ 5 mL/min).
CAZ: ceftazidime; AVI: Avibactam
Source: Table 27, Clinical Pharmacology review

Based on the lower clinical cure rate in patients with moderate renal impairment receiving the originally proposed dosing regimen, lower predicted ceftazidime and avibactam exposures in patients with moderate or severe renal impairment compared to patients with normal renal function, and the Fortaz label[2] recommending a 50% increase in ceftazidime dose for renally impaired patients with severe infections, Dr. Jang recommends that the originally proposed dosing regimen be revised.

[2] http://www.accessdata fda.gov/drugsatfda_docs/label/2014/050578s055,050634s023lbledt.pdf; accessed February 04, 2015

The revised dosing regimens for patients with renal impairment proposed by the Applicant as shown in Table 4 are predicted to result in ceftazidime and avibactam exposures in patients with CrCL ≤ 50 mL/min similar to those in patients with normal renal function receiving 2000 mg ceftazidime and 500 mg avibactam q8h, but lower than patients with mild renal impairment receiving 2000 mg ceftazidime and 500 mg avibactam q8h. Dr. Jang finds this proposal acceptable and notes that although other regimens were considered, the proposed regimen is considered appropriate as it provides an advantage in terms of probability of target attainment in patients with rapidly changing renal function in whom the dose is not readjusted. As the exposure of both ceftazidime and avibactam is highly dependent on renal function, it will be important to monitor CrCL frequently and adjust the ceftazidime-avibactam dose accordingly.

Table 4: PK parameters predicted from simulated cIAI patients (receiving the revised dosing regimens)

Renal Function	Revised Dosing Regimen	Ceftazidime		Avibactam	
		$C_{max,ss}$ (μg/mL)	$AUC_{0-24,ss}$ (μg·h/mL)	$C_{max,ss}$ (μg/mL)	$AUC_{0-24,ss}$ (μg·h/mL)
NORM	2000 mg CAZ + 500 mg AVI, q8h	45.5 (63)	518 (63)	9.17 (62)	91.2 (62)
MILD	2000 mg CAZ + 500 mg AVI, q8h	57.6 (63)	783 (64)	11.0 (62)	126 (63)
MODE	1250 mg CAZ + 250 mg AVI, q8h	39.5 (63)	643 (64)	7.87 (62)	116 (63)
SEV1	750 mg CAZ + 188 mg AVI, q12h	34.6 (63)	571 (64)	7.61 (62)	118 (64)
SEV2	750 mg CAZ + 188 mg AVI, q24h	38.6 (64)	628 (65)	9.70 (63)	158 (66)
ESRD	750 mg CAZ + 188 mg AVI, q48h	59.6 (67)	1120 (69)	7.78 (62)	111 (62)

NORM (CrCL > 80 mL/min); MILD (CrCL 51 mL/min to ≤ 80 mL/min); MODE (CrCL 31 mL/min to ≤ 50 mL/min); SEV1 (CrCL 16 mL/min to ≤ 30mL/min); SEV2 (CrCL 6 mL/min to ≤ 15 mL/min); ESRD End-stage renal disease (CrCL 0 mL/min to ≤ 5 mL/min).
CAZ-Ceftazidime, AVI-Avibactam
Source: Table 29, Clinical Pharmacology review

The following table summarizes the final recommended dosage regimens for ceftazidime-avibactam as a function of renal impairment:

Table 5: Recommended Dosing Regimens

Estimated Creatinine Clearance (mL/min)[a]	Dosing Regimen (ceftazidime/avibactam)
Greater than 50	No dosage adjustment necessary
31 to 50	1.25 grams (1 grams/0.25 grams) intravenously (over 2 hours) every 8 hours
16 to 30	0.94 grams (0.75 grams/0.19 grams) intravenously (over 2 hours) every 12 hours
6 to 15[b]	0.94 grams (0.75 grams/0.19 grams) intravenously (over 2 hours) every 24 hours
Less than or equal to 5[b]	0.94 grams (0.75 grams/0.19 grams) intravenously (over 2 hours) every 48 hours

[a]As calculated using the Cockcroft-Gault formula; [b] to be administered after hemodialysis on hemodialysis days

Dr. Jang also recommends that the Applicant conduct a postmarketing study to evaluate the pharmacokinetics, efficacy and safety of the revised dosing regimen of ceftazidime-avibactam in patients with cIAI with CrCL ≤ 50 mL/min. As the PK parameters with the revised dosing regimen have never been studied in patients, the data collected from this study will be useful to determine if further refinement of the dosage regimens will be needed. This study will be included as a postmarketing requirement.

As noted in the labeling for ceftazidime, the presence of mild or moderate hepatic dysfunction had no effect on the PK of ceftazidime in individuals administered 2 g IV q8h for 5 days, provided renal function was not impaired. The PK of avibactam in patients with hepatic impairment has not been established. Avibactam does not appear to undergo significant hepatic metabolism. As both ceftazidime and avibactam do not undergo hepatic metabolism in vitro, and the major route of elimination is via the kidney, hepatic impairment is not expected to impact the PK of ceftazidime or avibactam. Hence, modification of the dosing regimen is not considered necessary in patients with impaired hepatic function.

Susceptibility Test Interpretive Criteria

The percent time that free-drug concentrations are above the MIC over a dosing interval (% fT > MIC) has been established as the PK/PD index associated with efficacy of ceftazidime. The magnitude of the PK/PD index for antimicrobial efficacy (PK/PD target) for ceftazidime is considered to be approximately 40% to 50% fT > MIC for infections due to Enterobacteriaceae and *P. aeruginosa*. Based on hollow-fiber and animal model experiments, the percent time that free-drug concentrations are above a threshold concentration (CT) over a dosing interval (% fT > CT) was associated with the ability of avibactam to restore the activity of ceftazidime against ceftazidime-nonsusceptible bacteria. The PK/PD target of avibactam of 50% fT > 1.0 mg/L was determined based on restoration of activity of ceftazidime against ceftazidime-nonsusceptible *P. aeruginosa* in neutropenic mouse thigh and lung infection models.

Population PK models for ceftazidime and avibactam were used to explore PK/PD relationships in the Phase 2 trials and to conduct simulations to evaluate the probability of joint PK/PD target attainment for ceftazidime and avibactam. Probability of target attainment (PTA) analysis was used to support the susceptibility test interpretive criteria. The PTA analyses demonstrated >90% joint target attainment with the proposed dose (2.5 g ceftazidime-avibactam; 2.0 g ceftazidime plus 0.5 g avibactam q8h infused over 2 hours) for MICs up to 8 mcg/mL (Table 6). The population PK models used in the simulations included the effect of the disease on the clearance of both ceftazidime and avibactam, with cIAI patients having greater clearance (and thus lower plasma exposure) than healthy subjects or those with cUTI. Hence, the PTA for cUTI is higher than the PTA for cIAI.

Table 6: Percentage of Simulated cIAI Patients Achieving PK/PD Targets

Ceftazidime-avibactam MIC mcg/mL	Percentage of Simulated Patients Achieving PK/PD Target [a, b, c]
2	98.9
4	98.9
8	98.1
16	50.8
32	1.3

[a] Ceftazidime 2 grams and avibactam 0.5 grams, q 8 h intravenously over 2 hours
[b] 5000 simulated cIAI subjects with normal renal function (CrCL > 80 mL/min)
[c] PK/PD target for ceftazidime is 50% fT > MIC and for avibactam is 50% fT > 1 mg/L
Source: Table 1, Clinical Pharmacology review

Surveillance data obtained from 8,640 US isolates of Enterobacteriaceae collected in 2012 showed the MIC values for ceftazidime-avibactam ranged from ≤ 0.03 to > 32 mg/L. The MIC90 value for ceftazidime-avibactam was reported as 0.25 mg/L. Therefore, at the proposed PK/PD breakpoint of 8 mg/L, 99.9 % of all US Enterobacteriaceae isolates would be considered susceptible to ceftazidime-avibactam. Among the 925 isolates that were non-susceptible (intermediate and resistant) to ceftazidime, the ceftazidime-avibactam MIC values ranged from ≤ 0.03 to 16 mg/L (MIC90 value of 1 mg/L). At the proposed breakpoint of 8 mg/L, 99.4% of US isolates of ceftazidime-non-susceptible Enterobacteriaceae would be reported as susceptible to ceftazidime-avibactam. The MIC90 for Enterobacteriaceae isolated from the two Phase 2 trials was 0.25 mg/L.

Very limited clinical data are available at MICs > 0.25 mg/L. The following table summarizes clinical outcomes by MIC for baseline Enterobacteriaceae isolates in the two Phase 2 trials:

Table 7: Clinical Outcome by MIC for Enterobacteriaceae in the Phase 2 Trials

Ceftazidime-avibactam MIC (mg/L)	mMITT Population Favorable Microbiological Response n/N (%)		ME population Favorable Microbiological Response n/N (%)	
	cUTI	cIAI	cUTI	cIAI
≤ 0.03	4/6 (66.7)	10/12 (83.3)	2/2 (100)	9/11 (81.8)
0.06	12/14 (85.7)	18/21 (85.7)	7/9 (77.8)	18/18 (100)
0.12	8/15 (53.3)	15/20 (75.0)	6/10 (60)	15/17 (88.2)
0.25	6/6 (100)	8/9 (88.9)	4/4 (100)	8/8 (100)
0.5		2/2 (100)		1/1 (100)
1		1/1 (100)		1/1 (100)
2		2/3 (66.7)		2/3 (66.7)
8		1/1 (100)		
>32		0/1 (0.0)		

In the two Phase 2 trials, the number of isolates of *P. aeruginosa* was very small. The susceptibility test interpretive criteria proposed by Dr. Jang and Dr. Goodwin and accepted by the Applicant are as follows:

Table 8: Susceptibility Interpretive Criteria for Ceftazidime-Avibactam

Pathogen	***Minimum Inhibitory Concentration (mg/L)***		***Disk Diffusion Zone Diameter (mm)***	
	S	*R*	*S*	*R*
Enterobacteriaceae	≤ 8/4	≥ 16/4	≥ 21	≤ 20
Pseudomonas aeruginosa	≤ 8/4	≥ 16/4	≥ 18	≤ 17

I agree with their recommendation. Although clinical data are very limited at the higher MICs, the proposed criteria are supported by PK/PD data and microbiology surveillance data. The interpretive criteria for *P. aeruginosa* are consistent with those of ceftazidime. For ceftazidime, the susceptible breakpoint of (b) (4) for Enterobacteriaceae is based on a dose of 1 gram every 8 hours and the intermediate category (MIC 8 mcg/mL) is based on a dosing regimen of

2 gram every 8 hours. As the highest dose of ceftazidime-avibactam is 2 grams every 8 hours and the PTA at an MIC of 16 is 50.8, an MIC value for the intermediate category cannot be supported.

Dr. Jang recommends approval of the NDA and I agree with his recommendation.

7.0 Clinical Efficacy and Safety

The clinical reviewer for this NDA is Benjamin Lorenz MD, and the statistical reviewer is Margaret Gamalo PhD.

Efficacy

The clinical data to support the efficacy of ceftazidime-avibactam include results from two Phase 2 trials, one each in cUTI (NXL104/2001, Trial 2001) and cIAI (NXL104/2002, Trial 2002). In these trials, there was no pre-specification of any formal hypotheses for inferential testing, and the statistical analysis was limited to descriptive data summaries. In addition, the NDA includes interim efficacy results from an ongoing open-label Phase 3 trial in patients with cIAI or cUTI caused by ceftazidime-resistant Gram-negative bacteria (Resistant Pathogen Study D4280C00006). The Applicant has also provided a literature review to assess the historical efficacy of ceftazidime in cIAI and cUTI.

Complicated Urinary Tract Infections

Trial 2001 was a Phase 2, prospective, multicenter, investigator-blinded, randomized trial to evaluate the efficacy, safety, and tolerability of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of adults with cUTI. Patients with an estimated creatinine clearance (CrCL) < 70 mL/min or receiving either hemodialysis or peritoneal dialysis were excluded. The primary objective of the study was to determine the microbiological response in the microbiologically evaluable population at the Test of Cure (TOC) visit, 5 to 9 days post-therapy.

Patients were stratified based on the presence or absence of pyelonephritis and randomized 1:1 to either ceftazidime-avibactam 625 mg (500 mg ceftazidime + 125 mg avibactam) IV q8h over 30 minutes or imipenem-cilastatin 500 mg IV q6h over 30 minutes. The dose of ceftazidime-avibactam used in this trial was less than the proposed dose of 2.5 grams (2000 mg ceftazidime plus 0.5 grams avibactam administered as a 2-hour infusion). Switch to oral therapy (ciprofloxacin 500 mg PO q12h) was allowed after completion of at least four days of therapy. The total duration of therapy was 7 to14 days. Overall clinical assessment, urinalysis, safety laboratory assessments, and quantitative urine cultures were performed at baseline, during IV therapy (Day 3, 4, or 5), at the end of IV therapy, at the TOC visit 5 to 9 days post-therapy, and at 4 to 6 weeks post-therapy (late follow-up or LFU). Patients who received more than one dose

of another potentially effective systemic antibacterial drug after obtaining a baseline urine culture were excluded from the study. In addition, patients who received more than one dose of a potentially effective systemic antibacterial therapy within 48 hours prior to obtaining a baseline urine culture were also excluded from the study.

A total of 135 subjects were randomized, 68 in the ceftazidime-avibactam arm and 67 in the imipenem-cilastatin arm; 44 (64.7%) patients in the ceftazidime-avibactam arm and 41 (61.2%) in the imipenem-cilastatin arm had pyelonephritis. Approximately 75% of patients were female and 80% were less than 65 years of age. *E. coli* was the most common pathogen isolated and was identified in 40 patients in the ceftazidime-avibactam arm and 41 patients in the imipenem-cilastatin arm. All 14 ceftazidime-nonsusceptible isolates were *E. coli.*

Drs. Gamalo and Lorenz considered the microbiologic modified intent to treat (mMITT) population as the appropriate primary analysis population as the ME population excludes patients based on post-randomization events. The mMITT population was defined as patients who received at least 1 dose of study therapy and had a pre-treatment urine culture containing $>10^5$ CFU/mL of at least one uropathogen. The microbiological and clinical outcome at the Test of Cure (TOC) visit in the mMITT population was considered as the primary endpoint consistent with the current draft guidance on developing drugs for complicated urinary tract infections.[3] Table 9 provides the clinical and microbiologic outcomes in the mMITT population.

[3] Draft Guidance: Complicated Urinary Tract Infections: Developing Drugs for Treatment http://www fda.gov/downloads/Drugs/Guidances/ucm070981.pdf; accessed February 04, 2015

Table 9: Clinical and Microbiological Response at TOC (mMITT Population)

	Ceftazidime-avibactam N=46 n (%)	Imipenem-cilastatin N=49 n (%)	Observed Difference (95% CI)*
Microbiological Response			
Eradication	31 (67.4)	31 (63.3)	4.1 (-16.1, 23.8)
Persistence	10 (21.7)	14 (28.6)	
Indeterminate	5 (10.9)	4 (8.2)	
Clinical Response			
Cure	37 (80.4)	36 (73.5)	7.0 (-11.6, 24.7)
Failure	5 (10.9)	9 (18.4)	
Indeterminate	4 (8.7)	4 (8.2)	
Clinical & Microbiological Response			
Cure + Eradication	29 (63.0)	25 (51.0)	12.0 (-9.1, 31.7)
Failure + Persistence or Indeterminate	17 (37.0)	24 (49.0)	

*Exact 95% Clopper-Pearson confidence intervals; Source: Table 3-13, Statistics Review

The current susceptibility test interpretive criteria in ceftazidime labeling are as follows [4]:

Table 10: Susceptibility Test Interpretive Criteria for Ceftazidime

Pathogen	Minimum Inhibitory Concentrations (mcg/ml)		
	Susceptible	Intermediate	Resistant
Enterobacteriaceae§	≤ 4	8	≥16
*P. aeruginosa**	≤ 8	-	≥ 16

§ Susceptibility interpretive criteria for Enterobacteriaceae are based on a dose of 1 gram q 8h. For isolates with intermediate susceptibility, use a dose of 2 grams every 8 hours in patients with normal renal function. *For *P. aeruginosa*, susceptibility interpretive criteria are based on a dose of 2 grams IV every 8 hours in patients with normal renal function.

Table 11 provides the results for the subgroup of mMITT patients who had baseline isolates that were not susceptible to ceftazidime (MIC ≥ 8 mg/L for Enterobacteriaceae and ≥ 16 mg/L for *P. aeruginosa*). The Applicant also provided analysis in the subgroup pf patients with ceftazidime-resistant pathogens at baseline. In the ceftazidime-avibactam group, 6/7 (85.7%) ceftazidime-resistant *E. coli* were eradicated. In the imipenem group, 1/1 (100%) *E. cloacae* and 8/10 (80%) *E. coli* that were ceftazidime-resistant were eradicated. Characterization of specific mechanisms of resistance for the ceftazidime-resistant isolates was not provided in the study report.

[4] http://www.accessdata fda.gov/drugsatfda_docs/label/2014/050578s055,050634s023lbledt.pdf; accessed February 04, 2015

Table 11: Clinical Response and Microbiologic Outcome at TOC (mMITT Population, Ceftazidime-nonsusceptible Isolates)

Outcome	Ceftazidime-avibactam n (%)	Imipenem-cilastatin n (%)
Overall Population	**N=46**	**N=49**
Cure + Eradication	29 (63.0)	25 (51.0)
Failure + Persistence or Indeterminate	17 (37.0)	24 (49.0)
Ceftazidime-nonsusceptible isolates	**N=14**	**N=18**
Cure + Eradication	8 (57.1)	7 (38.9)
Failure + Persistence or Indeterminate	6 (42.9)	11 (61.1)

Source: Tables 3-13, 3-17, Statistics Review

Although the cure rates in the ceftazidime-avibactam arm were numerically higher than that in the imipenem-cilastatin arm in the overall population and in those with ceftazidime-nonsusceptible organisms, no definitive conclusion about the efficacy of ceftazidime-avibactam can be drawn as no inferential testing was pre-specified. The cure rates in this trial were lower than that seen in contemporary cUTI trials. The exact reason(s) for the lower cure rates in this trial is not clear.

Complicated Intra-abdominal Infections

Trial 2002 was a multicenter, double-blind, Phase 2 trial in adults with cIAI, where patients were randomized to receive ceftazidime-avibactam plus metronidazole or meropenem. Patients who received systemic antibacterial drugs within the 72-hour pre-study period were excluded, unless the patient had a new infection (not considered a treatment failure) and had received no more than 24 hours of total antibacterial therapy (preoperatively prophylaxis) and/or postoperatively), or the patient was considered to have failed the previous treatment regimen. The protocol defined primary endpoint was the clinical outcome at the TOC visit, performed 2 weeks post-therapy in the microbiologically evaluable (ME) population. Drs. Gamalo and Lorenz considered the clinical outcome at the TOC visit in the mMITT population to be the primary endpoint as outlined in the guidance on developing drugs for complicated intra-abdominal infections.[5]

Patients were stratified by baseline severity of disease (APACHE II score < 10, and > 10 to ≤ 25) and randomized 1:1 to receive ceftazidime-avibactam (2 grams ceftazidime plus 0.5 grams avibactam administered over 30 minutes) plus metronidazole (500 mg IV q 8h) or meropenem 1 gram IV q 8h. The proposed dosing regimen for the cIAI indication is to administer ceftazidime-avibactam 2.5 grams (2 grams ceftazidime plus 0.5 grams avibactam) as a 2-hour infusion. The

[5] Complicated Intra-abdominal Infections: Developing Drugs for Treatment http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm321390.pdf; accessed February 12, 2015

treatment duration was 5 to 14 days. Clinical assessments were performed at baseline, daily during study therapy, at the discontinuation of study therapy, at the TOC visit, and at the late follow-up visit (4 to 6 weeks post-therapy).

Two hundred and four hospitalized adults (18 to 90 years of age) with a presumed (preoperative) or definitive (intraoperative or postoperative) diagnosis of cIAI were randomized, including 102 in the ceftazidime-avibactam arm and 102 in the meropenem arm. Approximately 75% of patients were male and 90% were less than 65 years of age. The site of infection was the appendix in ~ 47% and the stomach/duodenum in ~25% of patients. Most patients (~90%) underwent open laparotomy and 45% had generalized peritonitis. More than a third of the patients in the mMITT population had polymicrobial infections (64/174). The most common pathogens identified from intra-abdominal sites were *E. coli, K. pneumoniae, S. aureus, P. aeruginosa, B. fragilis* and *E. faecium.*

The clinical response rates in the mMITT population at the TOC visit are shown in Table 12.

Table 12: Clinical Response at TOC in the mMITT population

Clinical Outcome	**Ceftazidime-avibactam plus metronidazole N=85; n (%)**	**Meropenem N=89; n (%)**	**Observed difference (95% CI)***
Clinical Response	70 (82.4)	79 (88.8)	-6.4 (-18.0, 5.2)
Clinical Failure	15 (17.7)	10 (11.2)	

Source: Table 3-24, Statistics review * Normal approximation with continuity correction

In the subgroup of patients with ceftazidime-nonsusceptible organisms, clinical response rate in the ceftazidime-avibactam arm was numerically higher than that seen in the meropenem arm [90% (27/30) and 82.6% (19/23) respectively]. However, in the subgroup of patients with ceftazidime-susceptible organisms, clinical response rate in the ceftazidime-avibactam arm was lower than that seen in the meropenem arm [76.2% (32/42) and 88.7% (47/53) respectively] and also lower than that seen in the overall population. Clinical response rate in the subset of patients with ceftazidime-nonsusceptible isolates is shown in Table 13.

Table 13: Clinical Response at TOC (mMITT Population, Ceftazidime-nonsusceptible Isolates)

Outcome	Ceftazidime-avibactam plus metronidazole n (%)	Meropenem n (%)
Overall Population	**N=85**	**N=89**
Cure	70 (82.4)	79 (88.8)
Failure	15 (17.7)	10 (11.2)
Ceftazidime-nonsusceptible isolates	**N=30**	**N=23**
Cure	27 (90.0)	19 (82.6)
Failure + Indeterminate	3 (10.0)	4 (17.4)

Source: Table 3-24, 3-29, 3-30, Statistics review

The Applicant also performed analysis in the subgroup of patients in the ME population who had baseline gram-negative pathogens that were resistant to ceftazidime (MIC >8 mcg/mL) for both Enterobacteriaceae and *P. aeruginosa*; 43 patients (26 in the ceftazidime-avibactam arm and 17 in the meropenem arm). Favorable responses were seen in 25/26 patients in the ceftazidime-avibactam arm. Across both treatment groups, avibactam restored the activity of ceftazidime for all but four isolates (two in each treatment arm). All four isolates had ceftazidime and ceftazidime-avibactam MICs of ≥ 32 mcg/mL. The specific mechanism(s) of resistance in these isolates are not yet available.

Clinical cure rates in the ceftazidime-avibactam arm were numerically lower than that seen in the meropenem arm in the overall population and in those with ceftazidime-susceptible isolates. Cure rates in the ceftazidime-avibactam arm were numerically higher than that seen with meropenem in those with ceftazidime-nonsusceptible isolates. These are post-hoc analyses and the numbers of patients in the trial and in each of the subgroups is small. Findings should be interpreted with caution as they could represent a chance finding. Also, as no inferential testing was pre-specified, no definitive conclusions about the efficacy of ceftazidime-avibactam can be drawn from this trial. Once data from the Phase 3 trial are available and reviewed, we may have a better understanding of the reason(s) for this discrepancy.

In addition to the two Phase 2 trials, the Applicant provided interim data from an ongoing study in patients with ceftazidime-resistant organisms (Resistant Pathogen Study, D4280C00006). This is a Phase 3 multinational, multicenter, randomized, open-label, study in adults with cIAI and cUTI caused by ceftazidime-nonsusceptible gram-negative pathogens. Subjects are stratified by diagnosis (cIAI and cUTI) and region (North America and Western Europe, Eastern Europe, and the rest of the world) and randomized 1:1 to ceftazidime-avibactam or best available therapy (BAT). The dose of ceftazidime-avibactam used is 2.5 g (2.0 g ceftazidime + avibactam 0.5 g IV q8h infused over 2h). Of the 21 patients with cUTI who were treated with ceftazidime-avibactam, 19 (90.5%) were cures compared to 18/23 (78.3%) treated with comparators. One patient in the ceftazidime-avibactam arm had cIAI and was a success compared to 1/3 (33.3%) in

the comparator arm. Dr. Gamalo has also performed additional analyses pooling the two Phase 2 trials and the interim data from this study. As patients in these trials differ in many characteristics, caution should be exercised in interpreting the results of pooled analyses.

The Applicant also performed a meta-analysis of published articles assessing treatment of cUTI/cIAI with ceftazidime. Based on the 15 articles included in the meta-analysis in which ceftazidime was used to treat cUTI, microbiological response rates at TOC was 89.1% [95% CI: 85.0, 93.2%]) and clinical outcome rates were 90.4% [95% CI: 85.5, 95.4%] at TOC. The populations in these studies were similar to a ME population. Two studies were identified in cIAI. In both studies, the duration of therapy or the timing of assessment was not specified. The clinical response rate post-therapy was 86.1% (95% CI: 74.1, 98.0%). In general, the publications had several limitations with respect to trial design, treatment duration, timing of assessment, and analysis populations.

Phase 3 cIAI trial

In October 2014, the Applicant submitted topline results from the recently completed Phase 3 cIAI trial, a randomized, multi-center, double-blind noninferiority trial comparing ceftazidime-avibactam (2.5 g administered q8h as a 2h infusion) plus metronidazole (500 mg q8h) to meropenem (1 g q8h). Per the protocol, patients with CrCL of 31-50 mL/min at baseline were to have their dose adjusted to 1.25 g q12h for ceftazidime-avibactam or 1 g q12h for meropenem. Patients with severe renal impairment (CrCL ≤ 30 mL/min) were excluded.

The clinical cure rates at TOC in the mMITT population were 81.6% in the ceftazidime-avibactam plus metronidazole arm and 85.1% in the meropenem arm (treatment difference -3.5, 95% CI -8.6% to 1.6%). Although cure rates were lower in both arms in patients with CrCL ≤ 50 mL/min, the decrement was more marked in the ceftazidime-avibactam plus metronidazole arm. As only preliminary data are currently available, the reason(s) for the lower clinical cure rates in this subgroup of patients is not clear. One possible reason proposed is that in patients with rapidly changing renal function, appropriate dosage adjustments were not made and hence these patients might have been under-dosed.

Table 14: Clinical Cure Rate in the Phase 3 cIAI Trial by Baseline Renal Function (mMITT Population)

Creatinine clearance	Ceftazidime-avibactam + Metronidazole % (n/N)	Meropenem % (n/N)
Greater than 50 mL/min	85% (322/379)	86% (321/373)
30 to 50 mL/min	45% (14/31)	74% (26/35)

Microbiological modified intent-to-treat (mMITT) population included patients who had at least one bacterial pathogen at baseline and received at least one dose of study drug

Based on data available thus far, it appears that some patients with rapidly changing renal function might have been under-dosed as doses were not adjusted appropriately in these patients. As only preliminary data are available thus far, no conclusions can be drawn about the reason(s) for the decreased efficacy and higher number of deaths.

In addition to the lower clinical response rate noted above, there was also an imbalance in the number of deaths in the subgroup with CrCL ≤ 50 mL/min. Eight deaths were reported in the ceftazidime-avibactam plus metronidazole arm compared to three deaths in the meropenem arm. In patients with normal renal function or mild renal impairment five deaths were reported in each treatment arm. Based on the analysis conducted by the Applicant thus far, it appears that the etiology of the deaths was multifactorial. Information about the lower cure rate is included in the Warnings and Precautions section and information about the increased mortality is included in the Adverse Reactions section of the package insert to warn healthcare providers about this finding and to highlight the importance of close monitoring of renal function in these ill patients.

Dr. Gamalo has noted reservations with the data in her review and supports approval of this product for limited use. She notes that there may be evidence of efficacy in cUTI based on the numerically higher (not statistically higher) treatment responses against the comparators in the Trial 2001 and the Resistant Pathogen Study. Dr. Gamalo also notes that the cure rates in Trial 2001 were lower than that seen in published reports. For cIAI, Dr. Gamalo notes that overall ceftazidime-avibactam appears less effective than meropenem and also in the subgroup of patients with baseline pathogens that are ceftazidime-susceptible. In the subgroup of patients with ceftazidime-nonsusceptible baseline pathogens, cure rates in the ceftazidime-avibactam arm were numerically better than in the meropenem arm. Dr. Lorenz concluded that adequate evidence has been provided to support the approval of ceftazidime-avibactam for the treatment of adults with cUTI and cIAI when alternative treatments are not suitable. Dr. Lorenz also notes that there is insufficient data to support approval for the following “Limited Use” indication: treatment of aerobic gram-negative infections, including hospital-acquired bacterial

pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) and bacteremia, where limited or no alternative therapies are available. Dr. Shamsuddin, the cross-discipline team leader concurs with their recommendations for approval of ceftazidime-avibactam for the treatment of cIAI and cUTI in patients with limited treatment options. I agree with their assessment.

Safety

The safety of ceftazidime-avibactam was reviewed by Benjamin Lorenz, MD, Medical Officer. The safety database included 11 Phase 1 studies, two Phase 2 trials, and data from ongoing/recently completed Phase 3 trials. A total of 286 subjects have received either single or multiple doses of 2000/500 mg of ceftazidime-avibactam (217 subjects) or 500 mg of avibactam alone (96 subjects). The median duration of ceftazidime-avibactam therapy was 5 days.

Overall, in the ceftazidime-avibactam development program, 61 deaths have been reported, including seven in the Phase 2 trials (4 ceftazidime-avibactam, 3 comparator) and 54 in the ongoing/recently completed Phase 3 trials (11 comparator, 16 ceftazidime-avibactam and 27 treatment-blinded). There were no deaths reported in the Phase 1 studies. In the Phase 2 cUTI trial, there was one death reported (imipenem treatment group) and in the Phase 2 cIAI trial, six deaths were reported (four in the ceftazidime-avibactam treatment group and two in the meropenem treatment group). Six deaths have been reported in the open-label Study D4280C00006 (three each in ceftazidime-avibactam and comparator arms). Based on a review of the narratives provided, Dr. Lorenz concluded that deaths were attributable to underlying comorbidities, treatment failure and/or emergent infection.

In Trial 2001 (cUTI), there were seven Serious Adverse Events (SAEs) reported in the ceftazidime-avibactam arm compared to two in the imipenem-cilastatin arm and in Trial 2002 (cIAI), nine SAEs were reported in each treatment arm. No SAE was reported more than once in ceftazidime-avibactam treated patients. No SAEs were reported in the Phase 1 studies. One patient in the cIAI trial (ceftazidime-avibactam plus metronidazole group) and four in the cUTI trial (3 in the ceftazidime-avibactam group and 1 in the imipenem group) had SAEs considered related to study drug (hepatic enzyme increased; diarrhea; accidental overdose; renal failure, acute; and blood creatinine, increased). In the Resistant Pathogen Study (D4280C00006), eight SAEs were reported in 113 patients treated with ceftazidime-avibactam and eight SAEs were reported in 109 comparator-treated patients. None of the SAEs in either treatment group were considered by the investigator to be related to study drug. As of June 25, 2014, the cut-off date for the 120-day safety update, 228 SAEs were reported in 180 (6.8%) subjects in the ongoing blinded Phase 3 trials and 46 subjects discontinued study drug due to an adverse event (AE). Treatment group assignments in these studies remain blinded.

In the Phase 1 studies, the most frequent adverse events in all subjects receiving avibactam alone were headache, diarrhea, and application site bruise. One subject who received multiple doses of

avibactam 500 mg had a transient, asymptomatic increase of serum liver enzymes values on study Day 5 with transaminases exceeding 5× ULN (alanine aminotransferase [ALT] 339 to 522 IU/L, aspartate aminotransferase [AST] 165 to 246 IU/L, gamma glutamyl-transpeptidase [GGT] 107 to 154 IU/L on Days 5, Day 7, and Day 8 of the study). Three days after the last dose of study drug, levels were lower but not yet normalized (ALT 307 IU/L, AST 86 IU/L, GGT IU/L). The subject was asymptomatic during the time period the liver tests were abnormal and did not receive concomitant medications during the study. All other laboratory test results were within clinically acceptable limits. The subject did not return to the clinical unit for further evaluations and was considered lost to follow-up. In Trial 2001, Treatment Emergent Adverse Events (TEAEs) that were more common in the ceftazidime-avibactam arm compared to the imipenem arm were constipation (10.3%), anxiety (10.3%) and abdominal pain (8.8%). The dose of ceftazidime-avibactam used in this study was 0.625 grams IV q 8h which is lower than the proposed dose. In Trial 2002, TEAEs that were more common in the ceftazidime-avibactam arm compared to the meropenem arm were vomiting (13.9%), nausea (9.9%), and anxiety (5.0%). Most TEAEs were mild or moderate in severity.

Mean and maximum changes in QTcF were similar in the ceftazidime-avibactam and comparator arms. In Trial 2001, one subject in the ceftazidime-avibactam arm had QTcF values > 500 ms. and changes from baseline > 60 ms. based on the centrally read ECG values, but no associated cardiac TEAEs were reported. A thorough QT (TQT) study showed that ceftazidime-avibactam did not prolong the QT interval. The TQT study was reviewed by the interdisciplinary review team (IRT). The IRT recommended that language regarding the TQT study be included in Section 12.2 (Pharmacodynamics) of labeling.

No significant differences were seen between the treatment groups with respect to clinical laboratory evaluations. Transient elevations in serum transaminases were observed with similar frequency in the two arms. There were no cases that met Hy's law criteria. In the Phase 2 trials, the incidence of a positive Coombs' test was < 10% in both ceftazidime-avibactam and comparator arms (7.3% vs 2.4%, respectively in cIAI and 1.9% vs 8.3%, respectively in cUTI). No subject had laboratory evidence of hemolysis or other TEAEs representing hematologic disorders.

Based on review of the literature and a search of the FDA Adverse Events Reporting System (FAERS), the Applicant identified nonconvulsive status epilepticus (NCSE) as a safety finding that is not included in the ceftazidime labeling. NCSE is included in the labeling for certain cephalosporins. A warning will be included in the Warnings and Precautions section of the ceftazidime-avibactam package insert regarding central nervous system reactions, including NCSE. The Applicant also investigated five adverse events of special interest: liver disorders, diarrhea, hypersensitivity, hematologic disorders, and renal disorders. One subject in a Phase 1 study discontinued high-dose ceftazidime-avibactam (5 g) due to a TEAE of urticaria. One

subject with mild renal impairment in the renal impairment study (NXL104/1003) who received avibactam alone had a mild TEAE of CrCL decreased that recovered and was considered unrelated to study drug. Four additional subjects receiving avibactam in the same study had increases in creatinine, they were all in the ESRD group and creatinine elevations occurred between hemodialysis sessions. One subject receiving avibactam experienced a TEAE of increased transaminases that was considered mild in severity and related to study drug. In the Phase 2 trial, there was one SAE of hepatic enzyme increased that occurred in a patient treated with ceftazidime-avibactam in the cIAI trial. The patient had elevations of AST, ALT (both 2 × ULN), and alkaline phosphatase (4.7 × ULN) and resulted in prolonged hospitalization. The frequency of postbaseline ALT or AST values > 3, 5, or 10 × ULN were low and similar in the two treatment groups. No cases of *Clostridium difficile* associated diarrhea or anaphylaxis were reported in the Phase 2 trials. No patients had laboratory evidence of hemolysis or other TEAEs representing hematologic disorders. In Trial 2001 (cUTI), two patients in the ceftazidime-avibactam group had SAEs representing renal disorders (acute renal failure, renal impairment); both had renal comorbidities and the SAEs resolved without sequelae. In Trial 2002 (cIAI), an SAE of acute renal failure occurred in one subject in the meropenem group that led to premature discontinuation of study drug.

8.0 Labeling

Labeling recommendation from Sevan Kolejian, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) and Christine Corser PharmD, from the Office of Prescription Drug Promotion (OPDP) have been incorporated in labeling. The Applicant had previously submitted CAZAVI as the proposed proprietary name. This name was found unacceptable by DMEPA due to orthographic similarities and shared product characteristics with the proprietary name Cozaar. The revised proposed proprietary name of AVYCAZ was found to acceptable.

Given the limitations of the currently available data, the Indications and Usage Section of labeling includes a statement that AVYCAZ should only be used for treating patients with cIAI or cUTI who have limited or no alternative treatment options. The Clinical Studies section (Section 14) of the package insert states that the determination of efficacy of AVYCAZ was supported in part by the previous findings of the efficacy of ceftazidime for the treatment of cIAI and cUTI and that the contribution of avibactam to AVYCAZ was established primarily in vitro and in animal models of infection. As the two Phase 2 trials in cIAI and cUTI were not designed with any formal hypotheses for inferential testing against the active comparators, clinical outcome data are not described in the Clinical Studies section. Safety data from these trials are included in the Adverse Reactions section (Section 6) of labeling.

9.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. The Applicant submitted a request for deferral of pediatric studies with the NDA. The pediatric plan and deferral request were presented to the Pediatric Review Committee (PeRC) on January 14, 2015. The PeRC agreed with the deferral request as the product is ready for approval in adults. The proposed pediatric studies will be postmarketing requirements.

10.0 Other Regulatory Issues

Clinical Site Inspections

Dr. Janice Pohlman, MD MPH, provided a clinical inspection summary for this NDA. For Trial 2001 (cUTI), one domestic and one foreign site were selected for inspection based upon enrollment numbers. The preliminary classification for both inspections is Voluntary Action Indicated (VAI). At both sites, there were protocol violations such as timing of repeat urine culture and use of nonstudy antibacterial drugs. Dr. Pohlman notes that there are no issues with data integrity at either site. For Trial 2002 (cIAI), one domestic and one foreign clinical site inspection were requested. The inspection of the foreign site has not yet been completed. An inspection summary addendum will be generated after the inspection has been completed and the results evaluated by Office of Scientific Investigations (OSI). The preliminary classification for the domestic site is No Action Indicated (NAI) and data generated by this site were considered to be acceptable. Actavis P.L.C. was inspected and the preliminary classification is VAI, primarily related to monitoring practices during the course of the study. Problems with the Interactive Voice Response System (IVRS) randomization and assignment of study drug vials were not acted upon promptly. Dr. Pohlman notes that the Applicant performed an extensive drug reconciliation process and appears to have ensured that subjects received appropriate study drug treatment. (b) (4), the Contract Research organization (CRO) responsible for the malfunctioning IVRS was also inspected and preliminary classification for that inspection is NAI. Inspection classifications will be finalized when the inspection correspondence is issued to the inspected entity.

Advisory Committee Meeting

This NDA was discussed by the Anti-Infective Drugs Advisory Committee on December 05, 2014. Minutes of the meeting are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-

InfectiveDrugsAdvisoryCommittee/UCM432232.pdf. The four questions and the committee votes are noted below:

Q1: Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated intra-abdominal infections, when limited or no alternative treatments are available?

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed?

Vote: Yes: 11 No: 1 Abstain: 0

Q2. Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated urinary tract infections, including pyelonephritis, when limited or no alternative treatments are available?

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed?

Vote: Yes: 9 No: 3 Abstain: 0

Q 3: Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia) when limited or no alternative treatments are available?

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed?

Vote: Yes: 0 No: 12 Abstain: 0

Q4: Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of aerobic gram-negative infections (hospital-acquired bacterial pneumonia/ventilator-associated pneumonia and bacteremia) when no adequate treatment options are available?

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed?

Vote: Yes: 1 No: 11 Abstain: 0

11.0 Risk Management

Joyce Weaver, PharmD, was the reviewer from the Division of Risk Management. Dr. Weaver concluded that the risks that have emerged to date can be addressed in labeling and a Risk Evaluation and Mitigation Strategy (REMS) is not required at this time. Dr. Weaver also noted that the risk related to decreased efficacy in patients with creatinine clearance 30 to 50 mL/min is not understood at this time, and cannot be characterized until the data for these patients are analyzed. I agree with Dr. Weaver's assessment that safety findings with ceftazidime-avibactam have been adequately addressed in labeling and that a REMS is not required at this time.

Post Marketing Requirements (PMRs)

The Applicant has agreed to the following PMRs, and on February 11, 2015, submitted proposed timelines which were found to be acceptable.

PEDIATRIC PMRs:

1. Conduct a randomized, multicenter, multiple-dose, active- controlled trial to evaluate the safety and efficacy of AVYCAZ (ceftazidime-avibactam) in children from 3 months to less than 18 years of age with cUTI. The dose for this study will be determined upon review of the data to be submitted by June 2015 from a single-dose, multicenter, non-comparative study assessing the PK of AVYCAZ (ceftazidime-avibactam) in pediatric patients from 3 months to less than 18 years of age.

2. Conduct a randomized, multicenter, multiple-dose, active- controlled trial to evaluate the safety and efficacy of AVYCAZ (ceftazidime-avibactam) in children 3 months to less than 18 years of age with cIAI. The dose for this study will be determined upon review of the data to be submitted by June 2015 from a single-dose, multicenter, non-comparative study assessing the PK of AVYCAZ (ceftazidime-avibactam) in pediatric patients from 3 months to less than 18 years of age.

3. Conduct a trial to evaluate the pharmacokinetics, safety and tolerability of AVYCAZ (ceftazidime-avibactam) in children from birth to less than 3 months of age with late-onset sepsis.

PMRs UNDER 505(o):

1. Conduct a prospective study over a five-year period after the introduction of ceftazidime-avibactam to the market to determine if decreased susceptibility to ceftazidime-avibactam is occurring in the target population of bacteria that are in the approved ceftazidime-avibactam label.

2. Conduct a trial or submit data from the Phase 3 trial in cIAI to evaluate the pharmacokinetics, safety, and clinical outcomes in adult patients with baseline renal impairment (creatinine clearance of 50 mL/min or less) receiving AVYCAZ (ceftazidime-avibactam) dosing regimens adjusted for renal function.

12.0 Recommended Regulatory Action

I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of ceftazidime-avibactam for the treatment of adults with complicated urinary tract infections and complicated intra-abdominal infections when limited or no alternative treatment options are available. I also agree with the review team that adequate data have not been provided to support approval for the Limited Use indication of treatment of aerobic gram-negative infections, including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia, where limited or no alternative therapies are available.

This NDA is covered under Section 505(b)(2) of the Food Drug and Cosmetic Act and relies in part on the Agency's prior findings of efficacy and safety of ceftazidime. The contribution of the avibactam component was assessed primarily in in vitro studies and in animal models of infection. While the two Phase 2 trials provide some evidence for the activity of ceftazidime-avibactam, neither trial was powered for inferential testing and so no definitive conclusions regarding the efficacy of ceftazidime-avibactam relative to the comparators can be drawn. Limited clinical data demonstrating that the addition of avibactam restores the activity of ceftazidime was available from patients with cIAI and cUTI who had ceftazidime-nonsusceptible microorganisms identified at baseline.

Given the limitations of the currently available data, ceftazidime-avibactam should only be used to treat patients with cIAI or cUTI who have limited or no alternative treatment options. Labeling includes a statement in the Indications and Usage Section that this product should be reserved for use in patients who have limited or no alternative treatment options. The main safety concerns including decreased efficacy in patients with creatinine clearance of 50 mL/min or less are adequately addressed in the Warnings and Precautions and Adverse Reactions sections of the package insert. Although the data available thus far have limitations, given all the information submitted in the NDA and the need for new antibacterial drugs to treat patients with few or no therapeutic options, I recommend approval of this NDA.

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/s/

SUMATHI NAMBIAR
02/25/2015